HEALTH SERVICES UTILIZATION AND RESEARCH COMMISSION

Preparing for Future Possibilities in Genetic Testing

Background Paper
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ABSTRACT

Genetic testing is unlike other medical tests and technologies. It poses unique ethical, legal, and social issues that must be addressed in the development of public policy and laws governing its use. Because of its broad reach and implications, genetic testing also presents new challenges for our health system.

Demand for genetic testing is expected to increase in the next decade, due to the availability of better tests and treatments for rare genetic disorders as well as new predictive genetic tests for more common disorders such as breast cancer and Alzheimer's disease. In Saskatchewan, we are most likely to see an increase in demand for prenatal screening for Down's syndrome and Edward's syndrome, diagnostic testing for fragile X syndrome, and predictive testing for hemochromatosis. Testing of individuals with strong family histories of breast cancer, colon cancer, and cystic fibrosis appears to be next in line.

To respond appropriately to these demands, clear health policy and law – as well as system preparedness – are required. The Health Services Utilization and Research Commission (HSURC) recommends Saskatchewan Health adopt a general policy framework and criteria for implementing genetic testing services. Further, given Saskatchewan's geographic characteristics, HSURC recommends Saskatchewan Health explore provincial and interprovincial models when determining how best to organize and deliver genetic testing and related services. HSURC also recommends that health science colleges, health professional organizations and Saskatchewan Health provide education to providers and the public about genetic testing and associated service delivery issues.

1. INTRODUCTION

As early as 25 years ago, scientists predicted a 'genetic revolution' with social consequences parallelling the industrial revolution.[1,2] Genetic science has advanced rapidly since then, particularly through the Human Genome Project (HGP) – an international initiative to identify the structure, organization, and function of the estimated 30,000-40,000 genes that make up the human genome.[3-5] Earlier this year, the HGP announced scientists had assembled the first draft sequence of the human genome. A completed sequence of the human genome is expected by 2003.[3] Some scientists now predict most major genetic factors involved in human disease will be defined over the next five to 10 years.[6-8]

Of current debate is whether a genetics revolution is truly knocking at our door – and if there is, whether we should be welcoming it.[9,10] Based on recent advances in genetic science and test technology, some advocates believe we may soon be able to prevent future disease and better treat existing disease through population-based genetic testing.[11] There are those who encourage the widespread availability of genetic testing, heralding its potential benefits to the health of populations through improved diagnosis, risk assessment, primary prevention, and disease treatment.[12,13] Other scientists view the notion of a genetics revolution as 'hype'.[9,10,14,15] They argue that the determinants of diseases affecting the largest portions of the population are multifactorial and complex. These critics suggest that a genetic approach to common diseases is inherently limited in what it can do, since environmental influences on health (e.g., nutrition, social factors) are the main drivers of disease incidence.[9,15,16] Separating the genetic and environmental aspects of most diseases and intervening effectively to reduce burden will likely be ongoing challenges for many decades to come.[9] As well, given that long lags typically occur

before effective treatments for most diseases are discovered, it will take some time before new knowledge of genetic disease determinants reaches full clinical benefit.[9] Finally, other observers have raised concerns about the various ethical, social, economic, and legal issues related to genetic testing, and argue these must be sorted out before embracing the new science.[9,16,17]

Regardless of the exact nature in which genetic science develops over the next decade, many analysts anticipate accelerated demand for testing and treatment, as new discoveries and commercial interests create pressure to fast-track research into routine clinical practice.[6,17-22] They believe the unique implications of genetic testing must be addressed as soon as possible. In particular, they propose that public policy and regulations must be developed to ensure genetic services are given their proper place within the broad spectrum of health services, to reap the population health benefits of genetic science, and to minimize potential risks.[4,16,17,23,24]

2. BACKGROUND

In October 1999, the Health Services Utilization and Research Commission (HSURC) received a request from Saskatchewan's Minister of Health to identify those genetic tests most likely to be available, efficient, and effective in the next five to 10 years, and to suggest potential criteria for assessing the use of genetic testing within a publicly funded health care system. The Commission decided to first identify the relevant issues and examine options for action. The objectives of this paper, therefore, are to:

- Provide a context and overview of the public policy issues relevant to genetic testing;
- Identify elements of a policy framework that could be used to assess the value of providing genetic tests in the publicly funded health system;
- Identify appropriate assessment criteria for evaluating genetic tests; and,
- Identify genetic tests for which there may be demand in the near future, and preliminary data on their effectiveness.

For the purposes of this paper, genetic testing was defined as "the analysis of human DNA, RNA, chromosomes, proteins, or other gene products to detect disease-related genotypes, mutations, or phenotypes, or karyotypes for clinical purposes."[25] (See Appendix A for additional information on genetic testing definitions.)

We conducted a series of literature reviews for this paper, using a broad search approach. Articles were selected on the basis of (a) their current relevance; (b) their comprehensiveness and clarity in presentation of the issues; (c) their relevance to the Saskatchewan and Canadian context; and, (d) their authority in representing the views or observations of scientists, governments, or the public. For example, official government or medical organization and consensus statements were given greater consideration, as were systematic reviews. We examined and have attempted to accurately present the views of all stakeholders. See Appendix B for details of our searches.

3. LITERATURE REVIEW

3.1 Public Policy Issues in the Implementation of Genetic Testing

We identified several public policy issues related to genetic testing. These issues can be divided into two broad categories: (1) those dealing with the social, ethical, and legal implications of testing; and (2) those dealing with technical or clinical aspects of testing and system delivery considerations. Table 1 outlines these key issues and their implications for health policy.[i]

3.1.1 Social, ethical, and legal issues

Much of the literature we reviewed focuses on the complex ethical, social, and legal issues posed by genetic testing. This focus suggests there is a need for a clear public policy framework that will protect both individual and societal interests.

Eugenics/genetic selection. A key challenge for policy-makers is determining how to establish policy that is consistent with both individual and societal values regarding genetic abnormalities (Health Canada, 1999).[28] The Universal Declaration on the Human Genome and Human Rights symbolically characterizes the human genome as "the heritage of humanity" and recognizes that we all have a right to respect for our dignity and rights regardless of our genetic characteristics.[29] As more is learned about how genes vary and function, the temptation may arise to ascribe to them an overly deterministic influence in shaping human health and potential. The pursuit of social policies that limit or constrain reproductive freedom is one possible consequence. Eugenic-related policy statements from agencies such as UNESCO[29] and the American Society of Human Genetics[30] fundamentally support the principle of reproductive freedom and decry coercion based on genetic information. Recommendations from the Royal Commission on New Reproductive Technologies are consistent with these statements.[31]

Although genetic test results can be used to make decisions regarding reproduction and the termination of embryonic and fetal life, there currently is no universal consensus on this application of the science. Canadian surveys have shown that about three-quarters of Canadians think abortion should be available for couples if the fetus has a severe anomaly, but fewer would choose to undergo it for themselves.[31] Current Canadian law protects the rights of individuals to choose abortion.[32]

Informed consent and confidentiality. Explicit informed consent is a fundamental requirement to the provision of genetic testing.[33] Yet in a recent study of 177 patients undergoing genetic testing, pre-test counselling was provided to only 19 per cent of patients, and written informed consent was obtained from only 17 per cent.[34] Thus, the principle of informed consent (in this context, the agreement to proceed with a genetic test upon receiving information about its risks and benefits) is not being universally applied.[31] Ideally, health policy and law should balance need for genetic information with individual privacy.[35] Consent and confidentiality issues require that the patient and practitioner engage in thorough discussion and realistic planning before the test is conducted.[33]

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[i] One issue not specifically addressed here is that of gene patenting. For more information on the ethical and legal implications of gene patenting, see, for example, Caulfield, Cherniawsky, and Nelson (1996)[26] and Macklin (1999).[27]

Table 1. Summary of Genetic Testing Issues and Their Health Policy Implications

Social, Ethical and Legal Issues*	
Issue	*Policy Implications*
Eugenics/genetic selection	Policy should be consistent with individual and societal values regarding genetic abnormalities and individual autonomy.
Informed consent and confidentiality	Policy should require explicit informed consent (including pre- and post-genetic counselling) and identify those circumstances when a breech of confidentiality is warranted.
Testing of children	Policy should identify whether such testing be provided only in cases where effective preventive measures exist and define when and how children/adolescents should have a role in the decision-making process.
Discrimination and stigmatization	Policy should protect the public from discrimination and stigmatization. Genetic testing should be voluntary; require informed consent; and be equally accessible to all. Access to genetic information by insurers, employers, and others should be strictly regulated.
Technical, Clinical and Service Delivery Issues	
Issue	*Policy Implications*
Limitations in predicting genetic risks	Policy should identify criteria for how effective genetic tests must be at determining or predicting illness before being made available to specific patient groups or the entire population. To avoid unrealistic expectations, policy should foster provider and public understanding of the technical merits of genetic tests.
Therapeutic gap	Policy should provide guidelines outlining conditions under which genetic testing must lead to treatments proven to improve health outcomes, or whether it is sufficient that test results simply provide additional clinical information.
Psychological impact of testing	Policy should require that appropriate pre- and post-test counselling be an essential element of service delivery.
Organization of care	Policy should identify the respective roles of primary care and specialist physicians in providing clinical care. Policy should require the implementation of organized screening programs if testing becomes justified for broader segments of the population.
Keeping provider services up-to-date and effective	Policy should require that providers stay abreast of advances in genetic testing and related issues.
Laboratory quality assurance	Policy should require strict regulation of laboratory standards for genetic testing. Policy should require specific test criteria be met before allowing laboratories to offer tests for clinical purposes and, once licensed to perform tests, require labs to regularly meet proficiency standards.

*Note: Ideally, these issues should be addressed by federal and/or provincial legislation, with policy that is consistent with the law.

Three characteristics of genetic information are relevant to the ethical and legal responsibilities associated with informed consent and confidentiality issues:

- The implications of genetic information are simultaneously individual and familial;
- Genetic information is often relevant to future disease; and,
- Genetic testing often identifies disorders for which there are no effective treatments or preventive measures.[33]

Although control of all personal medical information, including genetic information, belongs to the individual,[33] predictive or risk-assessing genetic information is likely to be valued by other family members. Generally speaking, doctors are under a legal obligation to maintain the confidentiality of medical records. There are, however, three recognized exceptions to the duty of confidentiality: where there is consent by the individual, authorization of a court, or the risk of harm to third parties.[31] Although privacy legislation supports confidentiality of patient information and thus places the onus on individuals to inform their relatives of test results, physicians can face conflicting responsibilities to protect the privacy of individuals and at the same time fulfill their duty to warn relatives of risk.

Testing of children. Genetic testing of children is an important topic in clinical genetics and plays an integral role in pediatrics.[36] Genetic diseases are common in childhood: As many as 53 out of every 1000 children can be expected to have diseases with a significant genetic component (Baird et al. 1988; cited in Ross and Moon 2000[36]). Genetic testing of children, however, raises many issues, including the balance of control between physicians and parents, and the child's role in the decision-making process and future autonomy. Since genetic information often applies to families as much as the individual child, defining confidentiality (for whom and from whom) is further complicated by the role of parents in giving consent.[36] Many people advocate that health policy and law should protect the vulnerable who may be incapable of weighing information to make an informed choice about screening, or who may not be able to make an independent decision for themselves later in life.[17,25,37]

At present, the most heated debate about genetic testing of children is the appropriateness of susceptibility testing.[38] As the number of identified gene mutations that cause or contribute to disease increases, so too does the number of children (including adolescents) likely to be eligible for genetic susceptibility testing. There is general agreement that it may be beneficial to do susceptibility testing of children for conditions for which there are effective treatments.[17,39] For other disorders, however, concerns about psychological harm to the child and the lack of any effective childhood treatment have led others to recommend against testing children.[40]

Although parental control over these decisions is often assumed, many people advocate granting greater control to children as they become more mature.[38] In Canada, where most provinces have no defined age of consent, policies that restrict the access of minors to genetic testing run contrary to existing consent law (Caulfield, personal communication, June 2001).[41]

Discrimination and stigmatization. Genetic testing carries risk of social harm in the form of discrimination. Further, it poses the risk of stigmatizing certain population groups with characteristics of race, gender, and ethnicity that come to be associated with genetic disease. Thus it is generally recommended that health policy and law be designed to protect the public from discrimination and stigmatization.[11,33]

Insurance companies frequently require applicants to divulge all risk information and to sign a release form that gives the insurers access to health care records, which may include genetic test results. If a company finds that genetic test results have been concealed, a policy may be nullified.[33] Recent responses from the Canadian insurance industry to the mapping of the human genome have been conflicting. Some companies have indicated they would use genetic information to assess client risk, whereas others have denounced the idea.[42] In the United Kingdom, the Human Genetics Commission recently recommended an immediate moratorium on the use of the results of genetic tests by insurance companies.[43] Earlier this year, the U.S. introduced two genetic non-discrimination bills related to health insurance.[44]

The development of public policy that addresses privacy and discrimination in the workplace, as it specifically refers to genetic testing results, is even less advanced. In the U.S., for example, despite the introduction of several bills over the past decade, no federal legislation has yet been passed that explicitly addresses genetic discrimination in the workplace. It may be argued, however, that existing non-discrimination laws may be interpreted to include genetic discrimination. Analysts recommend that such policy be analyzed in light of the uncertainty about the future scope and impact of genetic testing and be placed within the context of existing disability laws and other genetic discrimination and privacy legislation.[45]

3.1.2 Technical, clinical, and service delivery issues

The literature suggests that in light of a variety of technical limitations and complex aspects of clinical application of genetic testing, public policy must establish clear standards for the selection and administration of genetic tests before being provided in a publicly funded system. Several analysts and advisory groups have recommended approaches to service delivery that will ensure high-quality, efficient testing, and have identified the need to educate the public and providers on the benefits and limitations of testing.

Limitations in predicting genetic risks. Genetic tests have a number of limitations relevant to the management and regulation of their use.[46] A key challenge for public policy-makers is to establish criteria for how effective genetic tests must be at predicting illness before they should be offered to specific patient groups or the whole of the population. To avoid unrealistic expectations, policy should ideally foster provider and public understanding of the technical merits of genetic tests.

Although genetic testing is commonly thought to be highly deterministic, it is, in fact, most often probabilistic.[47,48] A key limitation is that a test may not detect every mutation a gene may have. For example, mutations can occur anywhere, even in multiple locations, along a single gene. Moreover, not all mutations have the same effect. More than 800 mutations of the cystic fibrosis gene have been identified, some of which cause varying degrees of disease severity and others which appear to cause no symptoms at all. Also, in many cases, the test only detects the more common, not the rare, mutations. The result: Neither a positive nor negative test result provides a strong prediction about development of this disease.[46]

Another factor that limits the predictive power of genetic testing is the complex interplay between genetic predisposition and environmental influences. At present, susceptibility tests for diseases such as breast or colon cancer can provide only the probability that an individual may

or may not develop the disease. For many common disorders—including insulin-dependent diabetes, hypertension, and schizophrenia—research suggests no single gene is predominantly involved nor is it currently possible to test for the complex genetic and environmental combinations that increase risk of disease. Even if it were, experts estimate such results would account for only a small portion of those affected.[11] Alleles[ii] of single genes usually play a role in less than five per cent of people with common diseases such as breast cancer, colon cancer, and Alzheimer's disease.[11,49] The majority of inherited diseases are caused by diverse mutations scattered along the entire length of the affected gene(s).[50] Regardless of whether the genetic condition is associated with simple single-gene mutations or not, the interaction with environmental influences is a critical yet not completely understood factor.

The therapeutic gap. For many of the diseases and conditions now being diagnosed or predicted using genetic tests, there are no effective treatments available now or likely to be available for some time. The challenge for policy-makers is to determine the circumstances under which genetic testing should be approved only where effective treatments for the conditions already exist—and not simply to provide additional clinical information.

Currently, genetic testing of infants is well accepted where testing is reasonably accurate and highly effective treatments exist, as in the case of newborn screening for phenylketonuria (PKU). To assist in their reproductive decisions, individuals can be carrier-tested to determine their risk of passing on a serious untreatable disease (e.g., Tay-Sachs disease) to offspring. Prenatal diagnosis and termination of pregnancy can then be offered to avoid the birth of an affected child.[16,51,52] Policy development becomes more complex in the case of prenatal tests that could be used to predict adult-onset disorders (e.g., Huntington's disease) or, in the future, simply to test for increased susceptibility to a disease (e.g., breast and ovarian cancer).[11]

Current clinical approaches such as prophylactic surgery and monitoring for incipient disease may prolong life in people with inherited susceptibility to diseases like colon and breast cancer. The extent of improvement, however, has not been established and the effects on quality of life have not been studied.[9] For the vast majority of people affected by common diseases with a known genetic component, it is not currently possible to prevent the condition, or improve survival or quality of life if the condition develops. In most cases, effective treatments are either not available, or are not likely to be for many years after testing for disease is possible. Although the genes responsible for Huntington's disease, Duchenne's muscular dystrophy, and cystic fibrosis have been known for some time, there is still no effective treatment available.[11] Effective treatments for some genetic diseases do exist. In the case of hemochromatosis, for example, development of a treatment preceded the discovery of the condition's disease-causing gene.[9]

Psychological impact of testing. Genetic tests can reduce, but not eliminate, uncertainty.[48] Due to varying perceptions of genetic-based disease, testing, and test limitations, genetic test results can lead to several negative responses such as persistent worry, depression, anger, confusion, despair, and false reassurance.[46,48,52] These may, in turn, lead to inappropriate

[ii] An allele is one of the members of a gene pair, each of which is found on chromosomes; the pair of alleles determines a specific trait.

life decisions.[53] There is strong support in the literature for making pre- and post-counselling essential components of genetic services delivery, to minimize such consequences.

Counselling that is sensitive to individual characteristics such as perceived risk, psychological resources, and social support influences whether people will choose to be tested and how they react to test results.[52] The research suggests that adverse psychological reactions are uncommon when the testing program separates the offer of the test from the actual taking of the biological sample, and provides clear information and emotional support before and after testing.[52] Further research is required to determine the amount and type of information and support required for more widespread use of pre-symptomatic genetic testing.[52]

Organization of care. In the U.K., there are currently 12 regional genetic centres, serving populations of two to six million. The literature suggests that such regional models of service delivery that provide diagnosis, risk estimation, counselling, surveillance, and support are likely to ensure appropriate and efficient provision of genetic testing services.[51,54] These multidisciplinary centres operate under a "hub and spoke" structure that includes specialist clinics, clinics in district hospitals, and community facilities. Within this model, genetic counsellors serve as a critical link between primary care physicians and specialists. These professionals, typically trained at the post-graduate level, provide non-directive counselling and try to help people choose options appropriate to their needs.[54] Clinical and laboratory services also work closely together.[54] Such a framework is seen as necessary to avoid potential harms of testing.

Several analysts and providers have concerns about the way care is currently organized and the health system's ability to meet increasing demands for testing.[19,21] There are reports that specialist genetic services are struggling to cope with increased workloads in Canada and elsewhere.[21,55] In the U.K., the Royal College of Physicians identified a target of two full-time equivalent clinical geneticists per million-population in 1993.[19] In Canada, data on median times for counselling, case review, and associated clinical duties are collected to establish concrete estimates of the number of geneticists (or general practitioners) likely to be required to meet needs.[56] Such information could prove valuable in establishing policy regarding service standards.

Keeping provider services up-to-date and effective. Given the pace and breadth of advances in genetic science, providers working in all branches of medicine will be required to advise individuals about genetic issues.[57] Genetics will not remain the exclusive domain of genetic specialists and centres; every physician will need to become genetically literate. The literature emphasizes the importance of developing policy that promotes and ensures providers' education in such areas as identifying genetic anomalies, accessing genetic services, interpreting risk factors, understanding the science of genetics, and addressing patient advocacy issues.[54,58]

Acquiring and supporting genetic skills in primary care involves a multi-faceted approach that includes genetic counsellors, medical geneticists, educational programs, and computerized decision support.[57] Many observers have suggested the need to more actively involve primary care physicians in genetic service delivery,[10,21,57] with genetic counsellors envisioned as having a key role in educating primary care teams and specialists and serving as a liaison between

them.[54] Informed consent, confidentiality, and the potential for social harm and psychological distress are ethical issues physicians need to fully understand.[33] Equity of access is another policy issue likely to need attention, given wide practice variation in genetic testing in Canada.[33]

As system gatekeepers, general practitioners need to know how to communicate effectively with people and refer appropriately for specialized genetic services. There is a concern that, given the speed at which genetic science is advancing, it will be difficult for providers to stay sufficiently up-to-date to fulfill their informed consent obligations. Studies have shown that general practitioners tend to have a limited knowledge base in human genetics.[18,33] However, under Canadian law, physicians have an obligation to discuss with patients the potential legal, ethical, familial, and social ramifications of testing.[18,33] This is not an easy task given the complexity and probabilistic nature of much information. Current case law indicates that physicians have a legal obligation to inform individuals about the availability of prenatal testing in particular.[33] Further, as noted above, genetic testing can create conflict for a physician who has a duty to respect individual confidentiality, but who also feels the duty to warn family members of possible risk.[33] To protect themselves from the threat of malpractice, physicians must stay up-to-date in their knowledge and skills.[18]

Laboratory quality assurance. Because of the ethical, legal, and social issues associated with genetic testing and decisions made based on test results, most analysts recommend strict regulation of laboratory standards for genetic testing.[17,46] A recent U.S. study found that 15 per cent of hospital-based, independent, and research-based molecular genetic testing laboratories surveyed had sub-optimal quality assurance scores. The labs surveyed also varied widely in terms of their confidentiality policies, and the extent to which they provided genetic counselling and obtained informed consent.[39] The U.S. Committee on Assessing Genetic Risks recommended several measures to ensure high-quality laboratory services, including publishing the names of laboratories that have met proficiency and other requirements, and requiring genetics laboratories to provide reports in understandable form to non-geneticists.[17]

3.2 Health Policy

3.2.1 Canadian health policy

In Canada, there are currently no formal policies or regulations specific to genetic testing (although some existing laws are relevant to genetic testing).[4] The federal government recently proposed draft legislation to ban human cloning and regulate related research. The impetus for this legislation was the evidence and recommendations put forward by the Royal Commission on New Reproductive and Genetic Technologies in 1993.[31] The proposed legislation and regulatory body would focus on regulating the manipulation of human sperm, eggs, and embryos, and would potentially prohibit controversial activities such as human cloning. In its currently proposed form, the initiative would address only some aspects of genetic testing.

The Health Canada policy framework proposes human reproductive and genetic technologies be governed in a way that affords protection for those most affected, reflects Canadian values,

and fosters scientific advances that are in the public interest.[28] It proposes eight guiding principles:

- Individual choice;
- Balance between individual and collective interests;
- Equality;
- Protection of the vulnerable;
- Appropriate use of technologies for treatment;
- Non-commercialization of reproduction and reproductive materials;
- Accountability; and,
- Integrity.

In addition, it proposes a national ethical advisory body, as recommended by the National Forum on Health, be used to incorporate ethical review into policy development and regulatory processes.

In late 2000, Health Canada formed the Working Group on Genetic Testing for Late-Onset Diseases. Its mandate is to review current legislation, research, ethical and social aspects, economics, and clinical practice; identify knowledge and attitudes about late-onset diseases among the Canadian public and health professionals; and develop a surveillance system for monitoring the use of genetic testing for late-onset diseases in Canada. A final report from this group is expected in Spring 2002.

3.2.2 International health policy

Some industrialized countries, such as the U.K. and Australia, have had regulatory frameworks governing genetic testing in place for a number of years.[28] In the U.S., the Secretary's Advisory Committee on Genetic Testing (SACGT) was chartered in 1998 to advise the federal department of health on the medical, scientific, ethical, legal, and social issues related to genetic testing.[46] Its first tasks were to assess the adequacy of "oversight" (regulatory supervision) of genetic tests, recommend options for additional oversight, and ensure public access to quality genetic tests. The framework proposes the following overarching principles:

- One of the main goals of genetic testing is to improve the health and well-being of individuals and families. No test should be introduced in the market before it has been established that it can be used to diagnose or predict a health-related condition in an appropriate way.

- Individuals and family members considering genetic testing should have access to appropriate genetic education and counselling resources, to ensure they are equipped to make an informed decision about being tested.

- Because genetic education and counselling are critical to the appropriate use, interpretation, and understanding of genetic tests, both health providers and the public must be educated about genetics.

- Written informed consent must be obtained for tests requiring high scrutiny, or review.

- Federal legislation is needed to prohibit genetics discrimination in the workplace and the health insurance industry. Federal legislation is also required to protect the privacy of genetic and other medical information contained in medical records.

- The public must be involved in the ongoing debate and dialogue about issues surrounding genetic testing.

3.2.3 General health policy approach

In addition to the policy principles articulated within and outside of Canada, a variety of policy approaches have been adopted or recommended by government, analysts, and advisory groups. Both Health Canada[28] and the SACGT[46] recommend that consumers be involved in policy-making. Public participation yields more representative policy and has been shown to result in more effective implementation of screening programs in particular.[60] Inclusion of genetic specialists and other non-genetic health professionals, ethicists, and lawyers in the policy-making process is also considered critical.[25] Both Health Canada and the SACGT also recommend creation of central repositories or registries of genetic information that protect confidentiality (including test results and outcome data). Canadian policy-makers can look to Australia, Britain, and Europe for examples of registries and health surveillance systems, and the U.S. for legislation on genetic privacy.[61]

Reviewers have noted that most proposed approaches to health policy on genetic testing are cautious and restrained.[18] Some argue that genetic information is not necessarily different from other types of health information[62] and that critics' main concern about the potential for discrimination is not proven.[63] They suggest that a focus on gene tests per se (i.e., tests which involve DNA, RNA, or chromosomes) and policy that is designed to prevent discrimination may not be necessary, or may in fact be ineffective in reducing discrimination.[63] Some reviewers argue that a special regulatory framework, justified on the grounds that genetic test results have special moral implications (e.g., potential discrimination), should address only those gene tests that are known to have such implications.[63] Furthermore, they suggest that the regulatory framework should include non-gene tests that confer information with the same implications (i.e., potentially any radiological or biochemical test).[63]

Conservative approaches to genetic testing policy have also been criticized for their potential to prevent valuable health outcomes, by limiting access to tests and associated services.[12] It is expected that genetic science related to common disorders might lead to efficient screening strategies, by defining patient groups most likely to benefit.[7] Some argue conservative policy thus runs the risk of increasing health care costs or forfeiting possible system savings.[62,64]

3.3 Evaluation Criteria for Genetic Tests

General methods for evaluating any test for disease include the evaluation of benefits, harms, and costs, followed by a comparison of outcomes to determine whether the benefits outweigh the harms and whether the health outcomes are worth the costs.[65] The first step is a matter of science, whereas the second is based on societal values and priorities in a publicly funded system. Well-accepted criteria to be met before adoption of any diagnostic test, as well as

criteria for tests used to screen large numbers of the population, are detailed elsewhere (see, e.g., Eddy, 1991[65]; Eddy, 1992[66]; Grimshaw, 2001[67]).

3.3.1 Criteria specific to genetic testing

The first recommendation of the SACGT in the United States deals specifically with evaluation criteria for genetic tests.[46] According to this group, analytical validity, clinical validity, clinical utility, and social consequences should be the major criteria used to assess the benefits and risks of genetic tests. These recommended criteria are not all that distinct from classic test criteria and are consistent with criteria well understood and articulated by others.[23,68]

Considerations such as the relationship between the demand for testing and the perceived individual burden of disease, the technical difficulty of genetic tests, and the resource/benefit trade-off should also be taken into account.[69] Although cost-effectiveness is a classic evaluation criterion for tests, some experts argue that it should not be a requirement in the case of prenatal diagnostic screening technologies such as triple marker (maternal serum) screening or genetic amniocentesis programs.[32,70] They suggest that trying to achieve cost savings through genetic testing could be viewed as eugenic.

Some analysts recommend that population screening be conducted only in the context of properly designed programs with equitable access.[16,67] The American Society of Human Genetics suggests tests should have a 90-95% sensitivity rate before they are incorporated into routine genetic screening programs.[17] Several models of service delivery have been examined and provide important groundwork for implementing appropriate genetic screening programs.[71-74]

3.4 Genetic Tests of the Near Future

Kinmonth and colleagues[21] identify three specific areas in genetic testing where developments may offer potential benefits to patients:

- Better tests for uncommon conditions (i.e., simple inherited disorders such as cystic fybrosis or β-thalassemia);
- New tests for rare cases of common conditions (i.e., tests that can identify rare but highly penetrant[iii] mutations at a particular gene locus, to be distinguished from the more common mutations of the gene that are associated with smaller disease risks). Examples include breast cancer and early-onset Alzheimer's disease; and,
- New tests for common genetic contributions to common conditions (i.e., tests that will identify the specific risk or risk protection of low-penetrance gene alleles associated with common conditions). Scientists are trying to develop tests of this nature for various chronic diseases.

There will likely be a small increase in test demand in the first two areas over the next decade. Some analysts predict that by the year 2010, predictive genetic tests will be available for as many as a dozen common conditions, enabling those individuals so inclined to find out their

[iii] Penetrance refers to the proportion of individuals of a particular genotype that express its phenotypic effect in a given environment.

susceptibilities.[7] Others suggest that progress in the next decade will likely be greater for single-gene disorders,[73] and that individuals with a strong family history of a particular condition (e.g., breast cancer) will likely be the first to be eligible for predictive genetic tests. In the United Kingdom, analysts predict there will be a growth of about five to 10 per cent annually in the volume of genetic tests for single gene disorders.[54]

In recent Canadian media reports,[13,55] some genetics experts bemoan the state of genetic testing in Canada. They suggest tests for breast cancer mutations, colon cancer, and hemochromatosis should be more readily available to all Canadians through regional or provincial programs. A recent survey of Canadians found most favour the use of genetic testing for specific medical purposes, including determining the risk of transmitting a disease to one's children (91%) and determining future risk of acquiring a medical condition (91%).[76] A 1995 survey of Canadian doctors also found nearly 60 per cent supported the offering of carrier testing for cystic fibrosis to high-risk ethnic groups, and 96 per cent agreed testing should be covered by provincial health care systems (Wertz 1995; cited in Caulfield and Feasby 1998[77]).

For tests of common genetic contributions to common conditions, however, it is difficult to accurately predict future demand. Many experts estimate that such testing is probably at least 20 years away.[7,8,78] It is unlikely there will be many instances in which effective interventions will justify widespread screening in the next decade. Even when all susceptibility genes for a given disorder have been identified, it will still not be possible to predict the development of disease with certainty until all the relevant environmental risk factors have also been identified and the nature of the various interactions is completely understood.[78] Many recognize that crystal ball gazing is bound to yield inaccurate predictions.[8,79]

Table 2 presents a summary of the estimated growth in test demand for specific genetic tests (see Appendix C for specific disease and condition details). It is important to note this presentation does not reflect a systematic review of each test, but merely a preliminary overview. Its ultimate purpose is to present a broad snapshot of the future possibilities in genetic testing in Saskatchewan. A more exhaustive overview of genetic testing for these and other conditions is also available elsewhere (see Andrews et al., 1994, pp. 75-99[17]). Table 2 includes current recommendations regarding test use as well as descriptions of test effectiveness. Based on this information, as well as information on current test demands, disease prevalence, and extent to which these tests have been reported in the scientific literature and mass media, an estimate of the future test demand on the Saskatchewan health care system is also presented. Prenatal testing for Down's syndrome and Edward's syndrome, diagnostic testing for fragile X syndrome, and predictive testing for hemochromatosis are estimated to be in high demand in Saskatchewan in the next five to 10 years. Testing of individuals with strong family histories of cystic fibrosis, breast cancer, and colon cancer appears to be next highest in demand.

The marketing of such tests to physicians and the general public will likely influence future demands. So, too, will accurate scientific and media reporting, consumer knowledge, and counselling regarding test performance and disease treatment outcomes.

Table 2. Selected Genetic Tests Expected to be in Demand in the Next Five to 10 Years

Type of Test	Examples	Current Screening Recommendations (Bold text refers to consensus statements or guidelines)	Test Effectiveness	Anticipated Demand on Saskatchewan Health Care System
Pre-implantation (provides information to couples on chances of future child developing disease, during pre-implantation stage of development)	–	Not yet available	Not yet determined	Low
Prenatal (provides information to couples on chances of future child developing disease, during prenatal stage of development)	Cystic fibrosis	Offer to couples planning a pregnancy and couples seeking prenatal care **NIH Cystic Fibrosis Consensus Development Conference, 1999**[80]	90% sensitivity for CFTR gene mutations	Moderate
	Fragile X syndrome	Offer to couples planning a pregnancy and couples seeking prenatal care (on fetuses of known carrier mothers) **American College of Medical Genetics, 1994**[81]	Molecular testing considered "gold standard"	Low
	Down's syndrome (Trisomy 21) and Edward's syndrome (Trisomy 18)	Screening of all pregnant women in second trimester is appropriate **SOGC**[82] Screening women should be offered as part of a coordinated prenatal screening service[32]	• Detection rate: 60 to 70% • False-positive rate: 8 to 9.5% • False-negative rate: 30 to 40%	High (since the test is voluntary, the uptake rate is estimated to be between 40-50% of all pregnancies)
Pediatric diagnostic (provides information on chances of symptomatic child having disease)	Fragile X syndrome	Testing of symptomatic population recommended **American College of Medical Genetics, 1994**[81]	Molecular testing considered "gold standard"	High

Table 2, continued

Type of Test	Examples	Current Screening Recommendations (Bold text refers to consensus statements or guidelines)	Test Effectiveness	Anticipated Demand on Saskatchewan Health Care System
Adult diagnostic and predictive (provides information to symptomatic and asymptomatic adults about their chances of having or developing disease, respectively)	Cystic fibrosis	• Testing of general population and newborns not recommended • Offer test to adults with family history and partners of individuals with cystic fibrosis **NIH Cystic Fibrosis Consensus Development Conference, 1999[80]**	90% specificity for ΔF508 gene mutations	Moderate
	Alzheimer's disease	• Predictive testing of asymptomatic individuals not recommended • Not recommended for use in primary care evaluation of dementia • Testing may be appropriate for patients with suspected early-onset Alzheimer's disease • Testing may be appropriate for relatives of patients with early-onset Alzheimer's disease **NIH National Study Group (Post et al., 1997[53])**	Not yet determined	Low
	Breast cancer	Not recommended for population screening **NACHGR, 1994[83]** Recommended for with strong family history of breast cancer or early onset of breast cancer **ASCO, 1996[84]** Moderate to high risk individuals be referred for genetic services for further assessment **U.K. CFSG (Eccles et al, 2000[85])**	Not yet determined	Moderate (currently the single most common referral for genetic testing in Saskatchewan)

Table 2, continued

Type of Test	Examples	Current Screening Recommendations (Bold text refers to consensus statements or guidelines)	Test Effectiveness	Anticipated Demand on Saskatchewan Health Care System
Adult diagnostic and predictive (provides information to symptomatic and asymptomatic adults about their chances of having or developing disease, respectively)	Colorectal cancer	Not recommended for population screening (Coughlin and Miller, 1999[86])	Not yet determined	Moderate
	Hemochromatosis	• Not recommended for population screening • Recommended for symptomatic individuals as early as possible • Recommended for 1st degree relatives and spouses of known homozygous and heterozygous carriers (Bernard et al., 1995[87]; Cogswell et al., 1999[88])	Screening of mutations (C282Y and H63D) in the HFE gene: sensitivity 84-100%; specificity 63-94%	High
	Heart disease, diabetes, other cancers, major mental illnesses	Not yet available	Not yet determined	Low

4. GENETIC TESTING SERVICES IN SASKATCHEWAN

In Saskatchewan, existing medical genetic resources cannot meet the demand for testing. There are currently three waiting lists, each greater than one year in length: testing for hereditary cancers (one quarter of monthly referrals are for breast cancer screening); predictive and diagnostic genetic testing (e.g., hemochromatosis, Huntington's disease); and non-urgent referrals, mainly for children with developmental delay of unknown etiology (Lemire, personal communication, June 2001[89]). The province has one full-time medical geneticist for a population of about a million people. Manitoba—a province of similar population and demographics—currently employs five medical geneticists (Lemire, personal communication, June 2001[90]). In contrast to Alberta, British Columbia, Ontario, and Quebec,[55] Saskatchewan cancer clinics do not provide genetic testing for hereditary forms of cancer. Instead, testing is done in the Medical Genetics Department within the Saskatoon health district, with samples sent to other provinces for analysis. DNA-based samples for many other genetic disorders are also sent out-of-province for analysis.

Only a relatively small portion of the Saskatchewan population receives genetic testing and related services, largely under the umbrella of reproductive and prenatal health services. Apart from universal PKU screening of newborns, there are no formal genetic screening programs, primarily because the province lacks large groups of distinct sub-populations at risk for known genetic disease. Services are not delivered through coordinated programs and funding is presently directed through health districts. As a result, there are disparities in the availability of testing (Lemire, personal communication, March 2001[90]).

5. DISCUSSION

5.1 Future Demands for Genetic Testing

Our cursory review found the greatest level of support for prenatal screening for trisomies 18 and 21 (maternal serum (or triple marker) screening), diagnostic testing for fragile X syndrome, and testing of symptomatic individuals with strong family histories of hemochromatosis. Next in line appear to be susceptibility testing for breast cancer and colon cancer, and carrier screening for cystic fibrosis for families where this disease has occurred. These will require additional research and review of their more complex clinical, ethical, treatment, and cost implications. Elwood[91] has articulated a thorough model for assessing potential need and demand for breast cancer mutation testing in Canada. This review also suggests that although there may be significant increases in demand for specific genetic tests in the next decade, population-wide susceptibility testing is not likely to be justified within the same period.

5.2 Implications for Action

To address current limitations in genetic testing and to ensure stakeholders are prepared for future demand for genetic testing, policy-makers and system stakeholders will need to take action on several fronts. Now is the time to lay the foundation of effective policy and evaluation criteria. Small-scale test demands expected in the near future can be used to evaluate the

effectiveness of the policy and criteria developed. Now is the time for providers to acquire a strong knowledge base and skill set in genetic services, as they face increasing inquiries about genetic testing.[18] Consumers should be involved in debates relating to policy and regulatory frameworks. Thus, public education on genetic testing issues is essential. This should be a joint responsibility of providers and government.

5.3 Establishing Effective Provincial Policy and Evaluation Criteria

This review suggests that a firm legal foundation is necessary to facilitate effective policy development.[23] As a first step, it would be prudent to pursue regulatory issues both nationally and provincially. To avoid duplication of effort, these issues may be best addressed through broader initiatives (e.g., health information law generally). Next, and perhaps simultaneously, a clear policy framework must be developed. Although the elements of an appropriate policy framework are already articulated, they need to be adopted and implemented—ideally involving a diverse group of policy-makers, specialists, general practitioners, nurses, and the public. The initial work done by Health Canada[28] and examples set in the United States and the United Kingdom[25] would provide good starting points for policy development.

To prevent market forces, professional practice, and legal issues from driving utilization and reimbursement—and, consequently, standards of care—we recommend use of an evidence-based model of policy development. This policy process is characterized by evaluation of clinical studies and exploration of normative issues with professionals and the public, then implementation of standards of care derived from these sources.[68] The derived policy framework should be placed within a broader context of population health, so that priorities can be established for all health services, not just genetic health services. This will enable government to make funding decisions about specific services that meet established test criteria.

5.4 Creating Health System Preparedness

This review suggests even a modest increase in testing could greatly tax the existing Saskatchewan health care system, particularly in terms of medical genetic services. Saskatchewan falls below the suggested British standard of two geneticists per million-population,[19] and well below the supply of medical geneticists in Alberta and Manitoba. As a have-not province, Saskatchewan would be ill-advised to compete with other provinces for specialist services. In a country with large geographical distances between centres, it may be advisable to create interprovincial rather than provincial genetic laboratory centres. An efficiency and effectiveness comparison would be required to determine what level of testing would justify provincial or local provision of services.

This review suggests that, if population demands are sufficiently high to justify genetic testing, an organized program is the best approach. Until that time, it may make sense to create an advisory group to oversee the development and implementation of standards of care for genetic testing within the existing service delivery system. Such an advisory group could address the technical, clinical, and service delivery issues outlined earlier in this paper. To address issues regarding demands expected in the next decade (i.e., tests outlined in Table 2) a two-pronged approach may be most feasible. The advisory group may want to consult with patient groups to determine service expectations and needs. At the same time, systematic reviews and guidelines

regarding these tests should be identified and considered at the provincial and national level. This evidence should then be forwarded to the relevant health ministries for review in the interprovincial, provincial and local context, with the adopted policy framework and evaluation criteria used to determine whether services should be provided within the publicly funded system. As tests are approved, appropriate delivery mechanisms can then be designed.

This review also suggests a major element of system preparedness is up-to-date and knowledgeable health professionals. Providers are important educators of the public, and their professional education can help increase public awareness and understanding. Steps should be taken to involve primary care professionals more heavily in genetic counselling and to ensure the specialist-primary care physician interactions are effective and efficient. Other specialists (e.g., obstetricians, oncologists, cardiologists, neurologists, etc.) should also be involved, in addition to genetic specialists. Although governments can foster this process, self-regulated health care professionals and their representative organizations also have a responsibility to acquire the skills and knowledge necessary to cope with increased demand for genetic testing. Notable international partnerships have been established that can be used to efficiently deliver genetics education to providers. For example, the National Coalition for Health Professional Education in Genetics, a U.S. collaboration involving the American Medical Association and American Nurses Association, has developed a national genetics education initiative.[48]

6.0 CONCLUSION AND RECOMMENDATIONS

The ever-increasing amount of media coverage on genetics is forcing jurisdictions around the world to sit up and take notice. The media's contribution has, more often than not, overlooked genetics' inherent complexities, with news reports frequently painting a simple deterministic picture. Scientific and policy commentators are unquestionably polarized: Some are enthusiastic about the field's potential merits and possibilities, others cautioning that genetics is only one strand in the web of causation of disease. Forces both within and outside the scientific community will continue to create pressures to move genetic testing outside the laboratory and into clinical practice. Sectors likely to benefit financially can be expected to lobby for a genetic approach.

Policy-makers and health-system decision-makers must act now, to address today's realities and prepare for tomorrow's possibilities. Although we will, in the short term, experience increased demand for some genetic tests, the science supporting population-level testing is still likely more than 10 years down the road. We have a window of opportunity in which to act, while things are still on a manageable scale. By working now to establish the necessary policies and institute required changes in the health system, we can ensure that the inevitable growth in genetic testing proceeds in accordance with scientific evidence and in a way that enables us to reap its full potential.

Thus, the following recommendations are put forward:

Saskatchewan Health should develop a clear policy and regulatory framework for genetic testing.

Saskatchewan Health should work with federal and provincial agencies, health districts, and the general public to sort through the various policy, regulatory, and service delivery issues related to genetic testing. It is especially important that policy decisions be driven by evidence, in light of expected consumer demand and industry pressure for genetic testing. Quality standards for genetic testing must be developed and regulated, and a solid legal basis upon which to build policy is essential. Preliminary work by Health Canada, as well as that done in the United States and the United Kingdom, may serve as a useful starting point.

Saskatchewan Health should develop appropriate geographic models of service delivery.

Given Saskatchewan's geographic characteristics, Saskatchewan Health should explore provincial and interprovincial models when determining how best to deliver genetic testing and related services. With a small population spread over a large area, Saskatchewan should consider partnering with other western provinces for testing, while concentrating specialists and genetic counsellors in larger Saskatchewan centres. The latter would be consistent with the Fyke Commission's recommendation regarding location of specialized services.[92]

Health science colleges, health professional organizations, and Saskatchewan Health should provide education so providers, students, and the public understand the issues around genetic testing and so that tests are used and interpreted appropriately.

In particular, education about current genetic testing issues should be provided through:

- Curriculum developed by health science colleges for students;
- Continuing education provided by health professional organizations for primary care providers; and,
- Public education campaigns developed by Saskatchewan Health.

There are several good international examples from which Saskatchewan can learn and borrow.

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APPENDICES

Appendix A
Genetic testing definitions

For the purposes of this paper, genetic tests are defined as "the analysis of human DNA, RNA, chromosomes, proteins, or other gene products to detect disease-related genotypes, mutations, or phenotypes, or karyotypes for clinical purposes. Such purposes include prediction of disease risks, identification of carriers, monitoring, diagnosis or prognosis, and establishing genetic identity, but do not include tests conducted purely for research."[25]

Genetic tests are usually classified into several types based on their timing and purpose:[17,31,46,52]

- *Pre-implantation/fertilization* tests for genetic mutations existing within an embryo;
- *Prenatal* tests for genetic mutations in a developing fetus (e.g., Down's syndrome)
- *Newborn* tests for genetic mutations at birth that are associated with diseases that can be treated effectively before negative effects (e.g., PKU);
- *Carrier detection* tests for genetic mutations that may be passed on to offspring and contribute to diseases (e.g., cystic fibrosis);
- *Diagnostic/symptomatic/confirmatory* tests to identify or confirm the diagnosis of a disease or condition in an affected individual (e.g., myotonic dystrophy);
- *Predictive/susceptibility/pre-symptomatic* tests to determine the probability that a healthy individual with or without a family history of a certain disease might develop that disease (e.g., Huntington's disease).

A variety of technologies are used in genetic testing, including counting and analyzing chromosomes in cells (*cytogenetics*), measuring protein products and metabolite levels in the blood (*biochemical analysis*), and using molecular genetic techniques to identify altered genes and mutations in the human genome (*linkage analysis, DNA sequencing, etc.*).[16,48] Samples may come from blood, amniotic fluid, or other tissue.[17] Other technologies such as ultrasound imaging are also used to assist in the diagnosis of diseases with genetic origins, such as Down's syndrome and polycystic kidney disease.[17] Some observers suggest that genetic testing policy must address these tests, in addition to those falling under the more narrow definition provided above.[63]

Appendix B
Literature search methods

Public policy issues in the implementation of genetic testing

We conducted a Medline literature review to identify public policy issues relevant to the implementation of genetic testing (keywords = genetic screening AND planning AND review; public policy AND genetic screening AND review; public policy AND genetic AND test; genetic AND test AND planning; genetic AND test AND issue*).

Health policy and evaluation criteria for genetic tests

To identify examples of specific criteria recommended for evaluating genetic tests, we conducted Medline and Internet searches of the health services evaluation literature and policy literature (keywords = public policy AND genetic AND test; health planning guidelines AND genetic AND test; needs assessment AND genetic AND test; community health planning AND genetic AND test). We also searched the "grey literature" (including government and organization Web sites) and HSURC's in-house literature.

Genetic tests of the near future

We conducted a Medline literature review to identify those genetic tests expected to be widely available in near future and their estimated effectiveness (keywords = genetic screening/*trends OR genetics, medical/*trends). To assess potential impact on service demand, we also tried to identify the size of populations at risk for the specific disorders being tested for. To locate current evaluations of test effectiveness, we searched several databases for recommendations, guidelines and systematic reviews including the Canadian Medical Association Infobase, the International Network of Agencies for Health Technology Assessment/National Health Service Centre for Reviews and Dissemination Database, and the Cochrane Library Database (Vol 1, 2001).

Appendix C
Diseases for which genetic tests are likely to be in demand in the next five to 10 years

Alzheimer's disease. Four genetic loci associated with Alzheimer's disease (AD) have been identified in the last decade. Three of these are disease-conferring (causal) genes, thought to represent less than two per cent of all AD cases,[48,93] and the fourth is a risk-conferring (susceptibility) gene, thought to contribute to as many as 50 to 70 per cent of all AD cases.[94]

For all types of genetic testing, including that for AD, the potential risks of testing—including discrimination, psychological distress, and difficulties associated with test disclosure among families—must be weighed against the potential benefits—including decreased uncertainty, psychological relief, and the ability to specify interventions aimed at preventing or treating disease.[48] With these risks and benefits in mind, a National Institutes of Health consensus conference concluded that predictive or diagnostic testing for the three disease-conferring genes is warranted, but only in patients with suspected early-onset, autosomal dominant AD.[53] They also noted that even in these cases, testing must be conducted with great caution in interpretation, and must adhere to formal informed consent procedures and pre- and post-test counselling. For the risk-conferring gene, they did not recommend the use of testing for predictive or even diagnostic purposes, due to the lack of sensitivity and specificity of the test and other factors.[53] Although the potential benefits of testing for the risk-conferring gene were not deemed to outweigh the potential risks, the consensus committee noted that the test might have diagnostic value in the future.[53]

Breast cancer. Breast cancer is the most frequently diagnosed malignancy in Canadian women. The mutations of genes BRCA1 and BRCA2 are considered responsible for about five to 10 per cent of all cases, particularly those that strike women in their 30s and 40s.[95,96] Women with these gene mutations have about a 60 per cent chance of developing breast cancer and about a 30 per cent chance of developing ovarian cancer. Proponents of testing suggest genetic testing for the gene mutations offers the advantages of increased surveillance (including breast mammography, prophylactic surgical removal of the breasts and ovaries, and chemoprevention), better management of already-existing breast cancer, and increased empowerment for patients.[96,97] One recent study showed that 48 per cent of at-risk women and 22 per cent of at-risk men requested presymptomatic genetic testing.[98] Of those women with an identified mutation, fifty-one per cent of those eligible for prophylactic mastectomy opted for the surgery, and 64 per cent of those eligible for oophorectomy chose to have it. To date, however, there is no clear evidence on the effectiveness of increased surveillance and chemoprevention.[95,99] Furthermore, major economic assessments of testing and treatment have yet to be published.[91] Recommendations for surveillance and prophylactic surgery are based only on expert opinion.[99]

Although many experts do not consider genetic screening of the general population to be warranted at present,[17] views on screening of the clinical population are mixed. Proponents of screening believe the key challenges for genetic services in the context of familial cancers are to identify those individuals at highest risk and to reassure those at low risk.[54] The American Society of Clinical Oncology recommends that genetic testing be made available to selected patients as part of the preventive oncologic care of families.[84] In particular, for instances in which patients have a strong family history of cancer or early onset of disease, the test can be

adequately interpreted, and results will influence the management of patients or family members, testing would be considered appropriate. Similarly, guidelines from the United Kingdom Cancer Family Study Group recommends that moderate to high-risk patients be referred for genetic services for further assessment.[85] A Canadian algorithm that categorizes women's hereditary risk of breast cancer as low, moderate, or high also recommends that high-risk women be referred for genetic counselling and consideration of genetic testing.[100]

In contrast, the National Advisory Council for Human Genome Research concluded in 1994 that until more information is available, it is premature to do DNA testing or screening for cancer predispositions outside a carefully monitored research environment.[83] These authors note there is a need for guidelines that are based on a comprehensive review of all aspects of testing. Many authorities have suggested that a 10 per cent prior probability of cancer is an appropriate cut-off, i.e., testing families with two or more breast cancer cases under age 50 or two or more ovarian cancer cases under age 60. A 50-per-cent threshold would include only families with at least four cases of breast cancer and one of ovarian cancer.[101] At present, clinics tend to use criteria to identify who is eligible for testing. (Saskatchewan, for example, follows the Ontario Cancer Genetics Network criteria for breast cancer.) Eligible women typically include those in families with multiple cancer cases, those who were young when diagnosed with cancer, or those with combinations of cancers, such as breast and ovarian cancers.[101]

Colorectal cancer. Hereditary nonpolyposis colorectal cancer (HNPCC), the most common type of inherited colonic cancer, has an autosomal dominant pattern of inheritance with variable expression. The nonpolyposis syndromes may account for over five per cent of colonic cancer.[86] Mutations of the hMSH2 gene and the hMLH1 gene account for 80 to 90 per cent of HNPCC cases.

Because it is not yet possible to conclusively identify gene carriers, diagnosis of HNPCC is still done clinically. Both the AHCPR and the Cancer Genetics Studies Consortium recommend that persons who fit the clinical criteria for HNPCC undergo colonoscopy at 20-25 years of age and be referred (along with family members) for genetic counseling.[102] Although genetic tests for susceptibility to HNPCC are becoming more widely available, they are not currently recommended outside of research protocols.[86] Since the predictive value of germline testing for mismatch repair gene mutation is only 50 to 80 per cent, colonoscopy should be performed regardless of test outcome in those cases where a mutation has not been identified in a family.[102]

Cystic fibrosis. In the early 1990s, a genetic test was developed for cystic fibrosis, a disease with high variability in the severity of its expression of symptoms and characterized by tenacious mucus in the lungs and mucus plugs in the pancreas.[80] There have been advances in treatment, but there is still no cure. The ΔF508 mutation accounts for 70 per cent of cystic fibrosis alleles, and testing for an additional 30 of the most common mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene is reported to have 90 per cent sensitivity in American Whites. In combination with other known cystic fibrosis mutations, testing sensitivities of 90-95 per cent can be achieved in specific populations such as Quebec French Canadians and Ashkenazi Jews. The knowledge of genotype, however, is of limited value in predicting clinical course for pulmonary function, which is the primary determinant of disease severity. Although data have shown that 50-78 per cent of at-risk couples would agree to prenatal diagnostic testing, far fewer people are in favour of population-level carrier testing.

There is no conclusive evidence that population-based neonatal screening yields medical benefit and cost savings. Many factors determine costs, but studies have shown averted cost per identified fetus to be $250,000 to $1,250,000. A National Institutes of Health consensus conference recommends genetic testing be offered to individuals with a family history of cystic fibrosis, to partners of those with cystic fibrosis, and to the prenatal population and couples currently planning a pregnancy (especially those from high-risk populations).[82] Testing for the general population and newborns is not recommended.

Fragile X syndrome. Fragile X syndrome is the single most common inherited cause of mental impairment. The prevalence rate in males is about twice that of females, affecting approximately one in 4,000 boys.[103] Testing for the causative mutation has become standard practice in children with developmental delays or behavioural problems.[81] Historically, testing for fragile X was done using a chromosomal or cytogenetic test. The two molecular DNA tests currently available are very accurate, enabling doctors to identify the genotype for both affected individuals and suspected carriers. Determination of fragile X syndrome is based on the number of repeated sequences of DNA material (also referred to as permutations) on the fragile X (FMR1) gene. Unaffected carriers have between six and 50 repeats of CCG (cytosine-cytosine-guanine), while individuals with more than 200 repeats have a full mutation and may be affected with fragile X. Allele sizes between 45 and 55 repeats are considered to be in the 'grey zone.' The American College of Medical Genetics does not recommend general population screening, but suggests testing should be considered for undiagnosed symptomatic individuals, carrier testing for individuals who have a family history of fragile X syndrome or undiagnosed mental retardation, and prenatal testing of known carrier mothers.[81]

Hemochromatosis. A disease characterized by a progressive iron overload that results in organ damage and dysfunction (liver, heart, pancreas), hemochromatosis is thought by some to be an ideal candidate for genetic testing due to the availability of simple, effective phlebotomy treatment.[88] It is now thought to be the most common genetic disorder in the general population. The genetic correlate of hemochromatosis was discovered in 1996, after effective treatments for the disease were already known. In one systematic review, however, analysts argue it is inappropriate to implement screening for hemochromatosis.[87] Genetic testing is typically based on screening for two mutations (C282Y and H63D) in the HFE gene. This test has a sensitivity of approximately 84-100 per cent and a specificity of approximately 65-94 per cent (Somerville, personal communication, June 2001[104]). The latter range corresponds to estimates of penetrance for this condition. The combination of high-risk genotype and altered blood chemistry is more compelling than either finding in isolation. Combining the two results has the potential to reduce the need for more invasive procedures such as liver biopsy. The main reason for not recommending screening was because a screening program was not considered feasible: Neither physicians nor the general population are aware of the disease, the acceptability of risk associated with diagnostic confirmation (liver biopsy) is low, and the compliance to the lifelong phlebotomies was estimated to be low. Despite 1996 recommendations from the American College of Pathologists in favour of screening, another review recommended against the practice because uncertainties remain about the penetrance and preventable burden of the disease, quality of laboratory standards, and optimal strategies to minimize potential risks of screening.[88]

Trisomy 21 and 18 (Down's syndrome and Edward's syndrome). In 1999, the Genetic Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) issued a committee opinion that provincially funded and centrally organized triple marker (maternal serum) screening for Down's syndrome and open neural tube defects should be implemented across Canada.[82] This has led to requests to provincial governments for funding of such programs.[32,93] The test, consisting of three components—alpha-fetoprotein (AFP), unconjugated estriol (uE3), and human chorionic gonadotrophin (hCG)—can detect 60-70 per cent of Down's syndrome cases and 60 per cent of Edward's syndrome cases for mothers of all ages.[32,82] A report from the British Columbia Office of Health Technology Assessment notes that although triple marker screening is cost-effective, this is not an ethical argument for endorsing screening; various social, personal, technical and professional factors have encouraged screening to proceed.[32]

Accuracy of the test relies heavily on accurate pregnancy dating, and therefore routine ultrasound dating is often recommended prior to screening.[32,82] Follow-up amniocentesis also is required for confirmation of Down's syndrome. The key advantage of triple marker screening is that a larger percentage of cases can be detected with less risk than when using age-based criteria (i.e., over 35) or tests which carry the risk of fetal loss (i.e., amniocentesis, chorionic villous sampling).[32] The primary disadvantage is that the procedure yields both false-positive test results (8-10% of fetuses will be falsely diagnosed with an abnormality) and false-negatives (approximately 30% of cases will go undetected).[32] For this reason, test counselling is considered critical, and delivery through an organized program desirable.[32,82]

Diseases for which effective testing is expected only in the very long term

Scientists have discovered genetic components to schizophrenia, manic-depression, autism, asthma, type 1 and type 2 diabetes, multiple sclerosis, and lupus, to name a few. However, the traditional method known to be most reliable in detecting rare single-gene disorders—linkage analysis—has proven much less reliable in studying these complex common diseases.[105] As a result, we may be further than once hoped from identifying susceptibility genes for these common diseases.[106] Test failure has been found to increase rates of false positive results, thus increasing risk of overdiagnosis of disease.[105,107]